Plasma pro-endothelin-1 (CT-proET-1) and respiratory distress in newborn infants

Jörg Benzing* M.D. (1), Oliver Stabile* (2), Gabor Szinnai M.D., Ph.D. (3), Nils G. Morgenthaler M.D., Ph.D. (4), Sven M. Schulzke M.D., M.Sc. (1), Christoph Bührer M.D., Ph.D. (5), Sven Wellmann M.D., Ph.D. (1,2)

(1) Division of Neonatology, University Children's Hospital Basel (UKBB), CH-4031 Basel, Switzerland

(2) Division of Neonatology, University Hospital Zürich, CH-8091 Zürich, Switzerland

(3) Pediatric Endocrinology, University Children's Hospital Basel, CH-8091 Basel, Switzerland

(4) Institute for Experimental Endocrinology, Charité University Medical Center, D-13353 Berlin, Germany

(5) Department of Neonatology, Charité University Medical Center, D-13353 Berlin, Germany

* Jörg Benzing and Oliver Stabile contributed equally to this work

Corresponding author: Dr. Sven Wellmann, Division of Neonatology, University Hospital Zürich, CH-8091 Zürich, Switzerland

Address: Frauenklinikstr. 10, CH-8091 Zürich, Switzerland; sven.wellmann@usz.ch; Tel.: +41 44 2555340; Fax: +41 44 255 4442

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Abstract

Plasma concentrations of the stable endothelin-1 precursor, CT-proET-1, determined prospectively in 293 newborn infants (gestational age 24 - 41 weeks) at birth and on day 3 of life, were unrelated to gestational age at birth but strongly associated with respiratory distress when measured on day 3 of life.

Introduction

Endothelin-1 is secreted by endothelial cells and acts as a potent vasoconstrictor (1). Raised plasma concentrations of endothelin-1 have been related to respiratory morbidity (1), including respiratory distress syndrome in newborn infants (2-5). Whereas endothelin-1 is unstable and therefore unsuited for diagnostic use, its secretion can be estimated by measuring CT-proET-1, the C-terminal portion of the endothelin-1 precursor (6, 7). The objective of this prospective study was to investigate the association between levels of circulating CT-proET-1 at birth and on day 3 of life and perinatal morbidity in preterm and term infants.

Subjects and methods

This cross-sectional study was performed between March 2009 and December 2010, enrolling a total of 293 infants born at the University Hospitals of Basel and Zürich, both Switzerland, after written informed parental consent. The Ethics Committees of Basel and Zürich approved the study protocol.

Blood samples were drawn from 256 umbilical veins at the time of delivery, with additional 83 paired samples from the umbilical artery and 90 paired blood samples from postnatal day 3. Samples were also taken from 37 unrelated infants on postnatal day 3 only. Blood sampling and processing as well as collection of clinical data have been described previously (8). Respiratory distress syndrome (RDS) was

classified according to chest x-ray findings. Bronchopulmonary dysplasia (BPD) was considered mild in infants requiring supplemental oxygen at a chronological age of 28 days, and moderate in infants requiring supplemental oxygen at a postmenstrual age of 36 weeks. CT-proET-1 (pmol/L) was measured in a single batch with BRAHMS KRYPTOR automated immunoflorescent assay (BRAHMS Biomarkers, Thermo Fisher Scientific, Hennigsdorf, Germany) (6). Continuous variables are reported as median (M) and range. Data were analyzed using Mann-Whitney U test, Kruskal-Wallis test, Fisher's exact test, and Spearman's rank order correlation coefficient (R_S) as appropriate employing SPSS 19.0 (SPSS, Chicago, Ill.). A p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of infants enrolled, split by gestational age (preterm vs. term), are shown in Table 1.

At birth, CT-proET-1 concentrations were unrelated to birth weight (BW) and gestational age (GA) (Fig 1A). Venous umbilical cord CT-proET-1 concentrations were consistently higher than matched arterial ones (M 148 vs. 134 pmol/L, $p<0.001$), but both values were closely related ($R_S=0.745$, $p<0.001$, $n=83$).

Umbilical cord CT-proET-1 concentrations ($n=256$) were slightly increased in infants with compromized placental perfusion (M 156 vs. 142 pmol/L, $p=0.015$, $n=137$) and infants born to mothers with preeclampsia (M 163 vs. 144 pmol/L, $p=0.032$, $n=256$). Delivery mode or signs of fetal distress immediately before birth (low arterial umbilical cord pH, suspect fetal heart tracing) and infections (i.e. maternal signs of infection at delivery, histologically proven chorioamnionitis, and neonatal bloodstream-proven sepsis) had no effect on CT-proET-1 at birth.

In contrast to CT-proET-1 at birth, CT-proET-1 on day 3 of life was inversely related to BW (R_S -0.610) and GA (R_S -0.649) (n=127, p<0.001) (Fig 1B), due to a profound postnatal increase in CT-proET-1 concentrations in preterm infants with respiratory morbidity. When investigating the association between CT-proET-1 and respiratory morbidity in preterm infants, we found that days of mechanical ventilation, continuous positive airway pressure (CPAP), and oxygen supplementation correlated each with CT-proET-1 level on day 3 (R_S 0.566, 0.658, and 0.819, respectively, for all p<0.001). Increasing levels of respiratory support in the first 3 days of life (none, CPAP only, endotracheal ventilation) were associated with increasing circulating concentrations of CT-proET-1 concentrations on day 3 (Figure 1C). A very similar association was found between degree of respiratory distress syndrome (radiological diagnosis) and CT-proET-1 concentrations on day 3 (Figure 1D).

Infants developing mild BPD had higher CT-proET-1 concentrations on day 3 than those without mild BPD (M/range 345 (219-537) pmol/L, n=11 vs. 194 (35-727) pmol/L, n=63; p<0.001), and infants developing moderate/severe BPD had higher CT-proET-1 concentrations on day 3 than those without moderate/severe BPD (387 (219-537) pmol/L, n=6 vs. 202 (35-727) pmol/L n=63; p=0.011). Multivariate logistic regression analysis, however, failed to establish CT-proET-1 on day 3 as an independent predictor of mild or moderate/severe BPD.

Discussion

This study demonstrates that CT-proET-1 concentrations in umbilical cord blood at birth are unaffected by GA (Fig 1A). Compromized placental perfusion appears to be associated with slightly elevated CT-proET-1 concentrations at birth. CT-proET-1 concentrations rose strongly from birth to day 3 of life in infants with RDS but not infants without respiratory disease (Fig 1C). Moreover, CT-proET-1 on day 3 of life was associated with radiological degree of RDS suggesting a dose-response relationship (Fig 1D). CT-proET-1, however, was not predictive of BPD after adjusting for GA.

An early increase in endothelin-1 has been shown to be a prognostic factor for BPD when endothelin-1 in tracheal aspirate was measured on day 7 of life (9). In our study, plasma CT-proET-1 concentrations were measured on day 3 of life which may reduce prognostic power compared to measurement on day 7. Moreover, we cannot exclude a type 2 error given that only 11 infants who had CT-proET-1 measurements on day 3 were diagnosed with mild BPD and 6 with moderate/severe BPD. It remains nevertheless intriguing to speculate that determining plasma CT-proET-1 within the first week of life may help to identify infants at risk of BPD. Functional data on endothelin-1 action (10) denote that endothelin-1 is not only a marker but a mediator of respiratory disease in newborn infants. These insights provide the framework for further studies investigating endothelin-1 action in newborn infants compromised by respiratory distress.

List of abbreviations:

CPAP	Continuous positive airway pressure
CT-proET-1	C-terminal prohormone ET-1
BW	Birth weight

GA	Gestational age
M	Median
RDS	Respiratory distress syndrome
BPD	Bronchopulmonary dysplasia

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Figure legend

Figure 1: Scatter plots of gestational age versus CT-proET-1 plasma concentrations in newborn infants determined at birth in venous umbilical cord blood (A) and at day 3 of life (B). Box (interquartile range) and whisker (5-95 % range) plots of CT-proET-1 plasma concentrations on day 3 in preterm infants (gestational age < 37 weeks) according to level of respiratory support (C) and severity of respiratory distress syndrome (RDS, D).

Table

Table 1. Subjects and perinatal characteristics

		GA 24-36 weeks		GA 37-41 weeks		
	n	n (%) or M (range)	n	n (%) or M (range)	n	p
Maternal characteristics						
- Signs of infection at delivery	293	32 (19)	165	1 (1)	128	<0.001
- Preeclampsia	293	45 (27)	165	3 (2)	128	<0.001
- Vaginal/abdominal delivery	293	127/38 (77/23)	165	77/51 (60/40)	128	0.002
Fetal characteristics						
- SGA (<5th P)	293	37 (22)	165	13 (10)	128	0.011
- Suspect CTG just prior to delivery	293	52 (32)	165	40 (31)	128	n.s.
Placentae, histological examination						
- Compromised perfusion	149	52 (40)	131	0 (0)	18	n.s.
- Chorioamnionitis	149	20 (15)	131	9 (50)	18	n.s.
Neonatal characteristics						
- Gestational age (weeks)	293	32.4 (24.4/36.9)	165	39.0 (37.0/41.9)	128	<0.001
- Birth weight (kg)	293	1.7 (0.4/3.7)	165	3.4 (1.9/4.8)	128	<0.001
- Arterial cord blood pH	274	7.31 (6.92/7.45)	153	7.30 (7.03/7.53)	121	0.001
- Apgar score at 5 min	293	8 (2/10)	165	9 (3/10)	128	<0.001
- Male gender	293	91 (55)	165	76 (59)	128	n.s.
Postnatal course until day 3 of life						
- Endotracheal ventilation	293	29 (18)	165	0 (0)	128	<0.001
- Any positive pressure support	293	79 (48)	165	0 (0)	128	<0.001
- RDS °1 or wet lung	293	60 (36)	165	0 (0)	128	<0.001
- RDS °2-4	293	38 (23)	165	0 (0)	128	<0.001
- Sepsis with positive blood culture	293	7 (4)	165	0 (0)	128	0.02
- PDA treated	293	31 (19)	165	0 (0)	128	<0.001
- Intraventricular hemorrhage >°1	120	6 (5)	120	0 (0)	0	n.s.
Postnatal course until discharge						
- Mild BPD	293	17 (10)	165	0 (0)	128	<0.001
- Moderate/severe BPD	293	8 (5)	165	0 (0)	128	0.011
- Death	293	9 (5)	165	0 (0)	128	0.006
CT-proET-1 (pmol/L)						
- At birth, venous cord blood	256	143 (34/328)	150	149 (63/230)	106	n.s.
- On day 3 of life	127	219 (35/727)	69	129 (38/189)	58	<0.001

GA, gestational age, SGA, small for gestational age; M, median; CTG, cardiotocogram, fetal heart rate tracing; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; mild BPD, oxygen until day 28 of life; moderate/severe BPD, oxygen at 36 weeks postmenstrual age. Characteristics were compared using Mann-Whitney U test or Fisher's exact test as appropriate. n.s., $p > 0.05$.

Figure

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Figure 1